

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/17255

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/12 C07K14/47 C07K16/18 A01K67/027 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C07K A01K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|--|
| X | SOOD R ET AL: "CONSTRUCTION OF A 1-MB RESTRICTION-MAPPED COSMID CONTIG CONTAINING THE CANDIDATE REGION FOR THE FAMILIAL MEDITERRANEAN FEVER LOCUS (MEFV) ON CHROMOSOME 16P13.3" GENOMICS, vol. 42, no. 1, 15 May 1997, pages 83-95, XP002066933 see table 1 | 6,9 |
| P,X | THE INTERNATIONAL FMF CONSORTIUM: "ANCIENT MISSENSE MUTATIONS IN A NEW MEMBER OF THE RORET GENE FAMILY ARE LIKELY TO CAUSE FAMILIAL MEDITERRANEAN FEVER" CELL, vol. 90, no. 4, 22 August 1997, pages 797-807, XP002066936 see page 800 | 1-4, 6-16, 18-20, 28-30, 32-34, 36-43 |

☒ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

22 January 1999

Date of mailing of the international search report

03/02/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
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Authorized officer

Smalt, R

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/17255

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|--|
| P,X | <p>FRENCH FMF CONSORTIUM: "A CANDIDATE GENE FOR FAMILIAL MEDITERRANEAN FEVER"</p> <p>NATURE GENETICS, vol. 17, no. 1, 1 September 1997, pages 25-31, XP002066935</p> <p>see the whole document</p> | <p>1-4, 6-16, 18-20, 28-30, 32-34, 36-43</p> |
| P,X | <p>BERNOT, A. ET AL.: "A transcriptional map of the FMF region."</p> <p>GENOMICS, vol. 50, 1998, pages 147-160, XP002090815</p> <p>see the whole document</p> <p>-& DATABASE EMBL - R55U031 Entry Hsaj03147, Acc.No. AJ003147, 22 January 1998</p> <p>BERNOT, A.: "Homo sapiens complete genomic sequence between D16S3070 and D16S3275, containing Familial Mediterranean Fever gene disease"</p> <p>XP002090820 From nt 208600-215910</p> | <p>8</p> |
| P,X | <p>BERNOT, A. ET AL.: "Non-founder mutations in the MEFV gene establish this gene as the cause of familial mediterranean fever (FMF)"</p> <p>HUMAN MOLECULAR GENETICS, vol. 7, no. 8, August 1998, pages 1317-25, XP002090816</p> <p>see table 1</p> | <p>12-16, 18-20</p> |
| T | <p>MCKUSICK, V.A. ET AL.: "Mediterranean fever, familial; MEFV"</p> <p>NCBI - ONLINE MENDELIAN INHERITANCE IN MAN, XP002090817</p> <p>http://www.ncbi.nlm.nih.gov/htbin-post/Omim/dispim?249100</p> <p>see the whole document</p> | |

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/ 17255

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 5, 17
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
Claims 5 and 17 have not been searched because none of the claimed sequences are amino acid sequences.
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark
Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

| | |
|--|--|
| Date of mailing (day/month/year) 26 May 1999 (26.05.99) | Applicant's or agent's file reference 11613.24WO01 |
| International application No. PCT/US98/17255 | Priority date (day/month/year) 21 August 1997 (21.08.97) |
| International filing date (day/month/year) 20 August 1998 (20.08.98) | |
| Applicant KASTNER, Daniel, L. et al | |

1. The designated Office is hereby notified of its election made:



in the demand filed with the International Preliminary Examining Authority on:

22 March 1999 (22.03.99)



in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

| | |
|--|---|
| The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35 | Authorized officer Lazar Joseph Panakal Telephone No.: (41-22) 338.83.38 |
|--|---|

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| | | |
|---|---|--|
| Applicant's or agent's file reference 11613.24W001 | FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. | |
| International application No. PCT/US 98/ 17255 | International filing date (day/month/year) 20/08/1998 | (Earliest) Priority Date (day/month/year) 21/08/1997 |
| Applicant THE GOVERNMENT OF THE UNITED STATES OF A. .et al. | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☒ **Certain claims were found unsearchable** (see Box I).

2. ☐ **Unity of invention is lacking** (see Box II).

3. ☒ The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing

☐ filed with the international application.

☒ furnished by the applicant separately from the international application,

☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.

☐ Transcribed by this Authority

4. With regard to the **title**, ☐ the text is approved as submitted by the applicant

☒ the text has been established by this Authority to read as follows:

THE PYRIN GENE AND MUTANTS THEREOF, WHICH CAUSE FAMILIAL MEDITERRANEAN FEVER

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

Figure No. _____ ☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/ 17255

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because they relate to subject matter not required to be searched by this Authority, namely:

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because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
Claims 5 and 17 have not been searched because none of the claimed sequences are amino acid sequences.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/17255

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/12 C07K14/47 C07K16/18 A01K67/027 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C07K A01K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|---------------------------------------|
| X | SOOD R ET AL: "CONSTRUCTION OF A 1-MB RESTRICTION-MAPPED COSMID CONTIG CONTAINING THE CANDIDATE REGION FOR THE FAMILIAL MEDITERRANEAN FEVER LOCUS (MEFV) ON CHROMOSOME 16P13.3" GENOMICS, vol. 42, no. 1, 15 May 1997, pages 83-95, XP002066933 see table 1 | 6,9 |
| P,X | THE INTERNATIONAL FMF CONSORTIUM: "ANCIENT MISSENSE MUTATIONS IN A NEW MEMBER OF THE RORET GENE FAMILY ARE LIKELY TO CAUSE FAMILIAL MEDITERRANEAN FEVER" CELL, vol. 90, no. 4, 22 August 1997, pages 797-807, XP002066936 see page 800 | 1-4, 6-16, 18-20, 28-30, 32-34, 36-43 |

☒ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

° Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

22 January 1999

Date of mailing of the international search report

03/02/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Smalt, R

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/17255

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|--|
| P, X | <p>FRENCH FMF CONSORTIUM: "A CANDIDATE GENE FOR FAMILIAL MEDITERRANEAN FEVER" NATURE GENETICS, vol. 17, no. 1, 1 September 1997, pages 25-31, XP002066935</p> <p>see the whole document</p> | 1-4, 6-16, 18-20, 28-30, 32-34, 36-43 |
| P, X | <p>BERNOT, A. ET AL.: "A transcriptional map of the FMF region." GENOMICS, vol. 50, 1998, pages 147-160, XP002090815 see the whole document -& DATABASE EMBL - R55U031 Entry Hsaj03147, Acc.No. AJ003147, 22 January 1998 BERNOT, A.: "Homo sapiens complete genomic sequence between D16S3070 and D16S3275, containing Familial Mediterranean Fever gene disease" XP002090820 From nt 208600-215910</p> | 8 |
| P, X | <p>BERNOT, A. ET AL.: "Non-founder mutations in the MEFV gene establish this gene as the cause of familial mediterranean fever (FMF)" HUMAN MOLECULAR GENETICS, vol. 7, no. 8, August 1998, pages 1317-25, XP002090816 see table 1</p> | 12-16, 18-20 |
| T | <p>MCKUSICK, V.A. ET AL.: "Mediterranean fever, familial; MEFV" NCBI - ONLINE MENDELIAN INHERITANCE IN MAN, XP002090817 http://www.ncbi.nlm.nih.gov/htbin-post/Omim/dispim?249100 see the whole document</p> | |

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

REC'D 10 JAN 2000

WIPO

PCT

A

| | | |
|---|--|---|
| Applicant's or agent's file reference GM5057 LGM/pe | | FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
| International application No. PCT/US98/17255 | International filing date (day/month/year) 25/08/1998 | Priority date (day/month/year) 21/08/1997 |
| International Patent Classification (IPC) or national classification and IPC C12N15/12 | | |
| Applicant THE GOVERNMENT OF THE UNITED STATES... et al. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 6 sheets, including this cover sheet.

- ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

| | |
|---|--|
| Date of submission of the demand 22/03/1999 | Date of completion of this report 29.12.99 |
| Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized officer Roscoe, R Telephone No. +49 89 2399 2554  |

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US98/17255

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-25 _____ as originally filed

Claims, No.:

3,5-8,11,13-15,17, _____ as originally filed
19-47

1,2,4,9,10,12,16, _____ as received on 26/11/1999 with letter of 26/11/1999
18,48-50

Drawings, sheets:

1/14-14/14 _____ as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, _____ pages:
☐ the claims, _____ Nos.:
☐ the drawings, _____ sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US98/17255

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | | |
|-------------------------------|------|--------|-----------------|
| Novelty (N) | Yes: | Claims | 1-5, 9-50 |
| | No: | Claims | 6-8 |
| Inventive step (IS) | Yes: | Claims | 1-5, 9-50 |
| | No: | Claims | 6-8 |
| Industrial applicability (IA) | Yes: | Claims | 1-39, 45, 48-50 |
| | No: | Claims | 40-44, 46, 47 |

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

1. Citations

The documents mentioned in the present International Preliminary Examination Report are numbered as in the search report, i.e. D1 corresponds to the first document of the search report etc.

The priority document pertaining to the present application was not available at the time of establishing this first written opinion. Hence, the current assessment is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this assumption is incorrect, documents D2-D5 cited in the search report could become relevant to the assessment of whether the present application satisfies the criteria set forth in Article 33(1) PCT.

2. Reasoned statement on Novelty, Inventive Step and Industrial Applicability (Section V)

2.1 Novelty (Art.33(2) PCT)

D1 is the only presently relevant prior art. Said document discloses a contig of genomic clones spanning the 250 kb interval reported to contain the FMF gene. Fig.2 of D1 shows the extent of the clones, whichever one of which turns out to comprise the pyrin gene certainly being suitable in size for use as a probe. It can be assumed, unless proven otherwise by the applicant, that at least one of these clones comprises the coding sequence of pyrin (applicant is requested to indicate the position of MEFV on Fig.2 of D1). Certainly at least one of the clones will contain MEFV sequence, and could thus be employed as a probe.

Thus, D1 anticipates claims 6-8. The authorized authority sees no reason why it should not be possible to use a 1 MB fragment as a probe in hybridization experiments.

2.2 Inventive Step (Art.33(3) PCT)

Given that D1 represents the closest prior art, the isolation of the MEFV gene has

to be considered inventive. Mere knowledge of the approximate position of the gene (within a 250 kb range) does not enable the isolation of the gene, especially in the case where the nature (and thus sequence features) of the gene is not known, and no simple selection methods for the gene are available. Thus all clear claims which relate to this subject-matter and are formally novel will also be considered inventive.

2.3 Industrial Applicability (Art.33(4) PCT)

For the assessment of the present claims 40-44 (since they can be construed to include transgene therapy), 46 and 47 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

3. Certain observations (Section VIII)

3.1 Clarity (Art.6 PCT)

The terms "MEFV" and "pyrin" have been coined by the applicant and are thus arbitrary definitions not known by the skilled person. Hence, these terms have to be accompanied by technical information (i.e. sequences) when present in the claims. This problem applies to a large number of the claims. For example, claim 1 lacks any technical features and effectively merely claims what applicant set out to find, not the results of his work. Similarly, a skilled person does not know what the rfp(B30.2) domain of MEFV is. It does not suffice for such information to be present in the application documents - the claims should not contain arbitrary definitions.

Nucleic acid fragments and peptide fragments of MEFV or pyrin, respectively cannot be considered to solve an invention-related problem and consequently cannot be considered unitary when they are not linked by structural or functional

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US98/17255

features. For example, claim 3 presumably can encompass any peptides resulting from the expression of a truncated MEFV gene. These will solve no problem and are not necessarily linked by common structural features. The same applies to the probes or primers of claim 6-10. Claim 3 is further considered to be problematic due to the open-ended definition of the DNA - a skilled person would have known how to isolate a 1MB piece of DNA comprising the pyrin mutant gene from an affected individual. Hence, the claim should be clarified as new claim 1 has been to avoid inventive step problems.

The level of stringency of hybridizations must be defined in the claims (e.g. claims 7 and 8).

Where amino acid positions are mentioned, it should be clear what sequence is being referred to so as to ensure that it is absolutely clear what the numbering refers to.

New claims

1. An isolated gene encoding only pyrin.
2. The gene of claim 1, comprising the coding sequence of SEQ ID NO:2, and variations thereof permitted by genetic code degeneracy.
4. The nucleic acid sequence of claim 3, comprising a mutant pyrin having an amino acid substitution in a rfp (B30.2) domain.
9. The nucleic acid primer of claim 6, wherein the primer is one of a pair of primers that amplifies MEFV.
10. The nucleic acid primer of claim 6, wherein the primer is one of a pair of primers that amplifies a nucleic acid sequence encoding a rfp (B30.2) domain of pyrin.
12. An amino acid sequence comprising a familial Mediterranean fever-associated mutant of pyrin.
16. The amino acid sequence of claim 12, wherein an amino acid substitution comprises a mutant selected from the group consisting of M680I, M694V, K695R, or V726A.
18. An amino acid sequence of pyrin comprising an rfp (B30.2) domain of pyrin.
48. Use of pyrin in the manufacture of a medicament for a medical treatment comprising producing pyrin in a host cell comprising transforming the host cell with a nucleic acid sequence encoding pyrin.
49. Use of the transgenic animal of claim 45 in a method of screening for a compound for use in medical treatment of FMF.
50. Use of the transgenic animal of claim 45 in a method of screening for a compound for use in medical treatment of inflammatory disease.

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| | | |
|---|-----------|---|
| (51) International Patent Classification ⁶ : C12N 15/12, C07K 14/47, 16/18, A01K 67/027, C12Q 1/68 | A1 | (11) International Publication Number: WO 99/09169 (43) International Publication Date: 25 February 1999 (25.02.99) |
|---|-----------|---|

(21) International Application Number: PCT/US98/17255

(22) International Filing Date: 20 August 1998 (20.08.98)

(30) Priority Data:
60/056,217 21 August 1997 (21.08.97) US

(71) Applicant (for all designated States except US): THE GOVERNMENT OF THE UNITED STATES OF AMERICA as represented by THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES [US/US]; Suite 325, 6011 Executive Boulevard, Rockville, MD 20852 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): KASTNER, Daniel, L. [US/US]; 10112 Ashburton Lane, Bethesda, MD 20817 (US). AKSENTIJEVICH, Ivona [US/US]; 5719 Beech Avenue, Bethesda, MD 20817 (US). CENTOLA, Michael [US/US]; 915 Prospect Street, Tacoma Park, MD 20912 (US). DENG, Zuoming [CN/US]; Apartment 304, 18207 Lost Knife Circle, Gaithersburg, MD 20879 (US). SOOD, Raman [CA/US]; 10203 Nolan Drive, Rockville, MD 20850 (US). COLLINS, Francis, S. [US/US]; 5908 Tudor Lane, Rockville, MD 20852 (US). BLAKE, Trevor [US/US]; 19814 Falling Spring Court, Laytonsville, MD 20882 (US). LIU, P., Paul [US/US]; 7725 Blueberry Hill Lane, Elli-

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(57) Abstract

The invention provides the nucleic acid sequence encoding the protein associated with familial Mediterranean fever (FMF). The cDNA sequence is designated as *MEFV*. The invention is also directed towards fragments of the DNA sequence, as well as the corresponding sequence for the RNA transcript and fragments thereof. Another aspect of the invention provides the amino acid sequence for a protein (pyrin) associated with FMF. The invention is directed towards both the full length amino acid sequence, fusion proteins containing the amino acid sequence and fragments thereof. The invention is also directed towards mutants of the nucleic acid and amino acid sequences associated with FMF. In particular, the invention discloses three missense mutations, clustered in within about 40 to 50 amino acids, in the highly conserved rfp (B30.2) domain at the C-terminal of the protein. These mutants include M680I, M694V, K695R, and V726A. Additionally, the invention includes methods for diagnosing a patient at risk for having FMF and kits therefor.

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